REMARKS / ARGUMENTS

1. STATUS OF CLAIMS

Claims 1-14, 52-54, and 57-62 are pending. Claim 57 is amended to delete a redundant "of the" in the claim.

2. EXAMINER'S OBJECTIONS

The Examiner objected to claims 57-62 because it recited "of the" twice. The claim has been amended to delete the redundant phrase. Applicant requests that the Examiner withdraw the Objection.

3. EXAMINER'S REJECTIONS

The Examiner, in a Non-Final Office Action mailed June 16, 2009, rejected all of the pending claims in the application.

A. Claims 1, 3-13, 52, 53, and 57-62 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Mitragotri et al., U.S. 5,814,599 ("Mitragotri"), in view of Royds et al., U.S. 5,466,465 ("Royds") and Unger et al., U.S. 5,580,575 ("Unger").

B. Claims 1-14, 52, 53, and 57-62 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Mitragotri, Royds, and Unger as applied to claims 1, 3-13, 52, 53, and 57-62 and further in view of Zeimer et al., U.S. 4,891,043 ("Zeimer").

4. ARGUMENTS AGAINST EXAMINER'S REJECTIONS

Applicant respectfully traverses the Examiner's rejections of claims 1-14, 52-54, and 57-62. Applicant requests reconsideration and withdrawal of the rejections based on the following remarks.

A. REJECTION OF CLAIMS 1, 3-13, 52, 53, AND 57-62 UNDER 35 U.S.C. § 103(a) AS BEING UNPATENTABLE OVER MITRAGOTRI IN VIEW OF ROYDS AND UNGER.

The Examiner asserts that Mitragotri discloses a method for enhancing drug delivery across the skin comprising applying the drug encapsulated in a liposome or polymeric microparticle to the skin and applying ultrasound to deliver the drug across the skin in a desired drug dosage. The Examiner acknowledges that Mitragotri does not disclose that the medium for holding the microparticles is placed on a surface of a patch adjacent to the skin.

The Examiner asserts that Royds teaches a transdermal drug delivery system comprising a patch wherein a matrix comprising microencapsulated particles of a drug leaches from the particles into the matrix and subsequently passes through the skin of the user. The Examiner acknowledges that Royds does not teach that energy, including ultrasonic energy, be used to selectively release the

drug from the microcapsules.

The Examiner asserts that Unger discloses a drug delivery system wherein microspheres are ruptured at the peak resonant frequency using ultrasound.

The Examiner concludes that it would have been obvious to one of ordinary skill in the art to combine these three references to obtain Applicant's claimed invention. Applicant respectfully disagrees.

Mitragotri discloses a method wherein ultrasound and proteins are simultaneously **applied to the skin surface** in order to deliver therapeutic doses of proteins across the skin [Abstract, col 3, ln 4-6]. Mitragotri defines the process, sonophoresis, as the application of ultrasound to skin on which a drug, comprising proteins, has been applied [col 4, ln 14-31]. In the preferred process, the drug is applied to the skin and ultrasound is applied immediately thereafter [col 5, ln 25-32]. Mitragotri exemplifies the process where in a glass chamber containing a solution of insulin is glued to a back of a rat and ultrasound is applied to allow the solution in contact with the rat's skin to penetrate [col 9, ln 6-19].

Mitragotri does not disclose or suggest that the protein-containing drug be placed "on a surface of a patch adjacent the skin of a human or animal" as recited in Applicant's claim 1. In fact, Mitragotri teaches away from the concept of having a patch layer between the skin and the applied drug. Mitragotri teaches that the application of the drug to the skin preferably occurs at a site on the body wherein the skin is relatively thin and has a high surface area to allow for maximum drug penetration [col 5, ln 25-32]. Mitragotri exemplifies only methods wherein the drug is in direct contact with the skin [Examples 3 and 5].

Royds discloses an occlusive patch that entraps sweat from the body, wherein the sweat both hydrates the skin and saturate a matrix comprising a drug in microencapsulated form, and wherein drug release from the microcapsules depends on the relative ease with which water from the entrapped sweat is able to penetrate the microcapsules" coat to dissolve the drug. The dissolved drug leaches from the microcapsule into the matrix and delivered through the skin to exert the desired effect [col 1, ln 56 to col 2, ln 8]. The process is controlled by either selecting the type of coating material for the microcapsule, or by manipulating the constituents of the coating material [col 5, ln 2-13]. Royds discloses that the patch comprises a translucent water-impermeable shell or backing layer [col 4, ln 31-42]. Royds discloses that the patch be occlusive (air- and water-tight) to enhance hydration of the skin [col 5, ln 50-55].

Royds does not disclose or suggest that ultrasound be used to stimulate release of the drug from the microcapsule.

Unger discloses a drug delivery system wherein ultrasound is applied to the region of the patient where therapy is desired, **after** the gas-filled microspheres have been administered to or have otherwise reached that region within the body. The gas-filled microspheres are ruptured by the ultrasound and release their

contents within the patient [col 2, ln 11-18], [col 18, ln 18-27].

Unger does not disclose or suggest that the method using gas-filled microspheres is applicable to microcapsules.

Unger also discloses that the gas-filled microspheres are also especially useful for transcutaneous delivery, such as a patch delivery system [col 17, ln 52-61]. However, Applicant asserts that within the context of Unger disclosure, such a patch delivery system is limited to introducing the microspheres into the body after which that region of the body is stimulated to rupture the microspheres to release drugs into the body. Applicant further asserts that this disclosure does not mean that ultrasound is used to stimulate drug delivery through the patch and through the skin to the targeted site within the body. Furthermore, Unger provides no instruction, teaching, or enabling disclosure on how a worker in the art may employ a patch for transcutaneous delivery of microspheres.

The focus of the disclosure of Unger is not transdermal administration of drugs, rather it is transdermal stimulation via ultrasound of microspheres within a body to cause rupture and release of drugs contained therein.

Applicant asserts that the methods of Mitragotri and Unger do not suggest the use of patches for introducing drugs through the dermis for treatment. Mitragotri teaches that it is preferred that the drug be in direct contact with the skin and stimulated to pass through the dermis. Unger teaches that the gas-filled microspheres are introduced into the body and ruptured via external stimulus of the skin with ultrasound. In Unger, the drug alone never passes through the dermis. Neither Mitragotri nor Unger provides any teaching or suggestion that drugs or gas-filled microspheres containing drugs may be added to a patch and the substances transferred through the patch and through the dermal layer for delivery into the body. Adding the disclosure of the patch of Royds does not overcome the aforesaid deficiency. Royds also does not teach nor suggest that energy, much less ultrasonic energy, be used to selectively release the drug from the microcapsules through a patch and through a dermal layer into the body.

Royds discloses that the microcapsules are placed in an occlusive patch before applying to the body and only after hydration leached through the surface of the skin. Royds also does not teach nor suggest irradiation as a method to release a drug from a microcapsule into a patch and ultimately through the skin. Royds discloses that the water solubility of the drug and permeability through the coating of the microcapsule allows it to be released into the patch and subsequently the body. There is no suggestion or reason for one of ordinary skill in the art to expect from the teachings of Royds that irradiation of the patch would affect the permeability of a drug through the coating of a microcapsule. Also, Mitragotri and Unger do not provide such a disclosure or suggestion.

Applicant therefore asserts that the combination of Mitragotri, Royds, and Unger fail to disclose or suggest to a person having ordinary skill in the art a "method for delivery of substance through at least one dermal layer…comprising

providing a substance in microcapsules within a medium..., placing the medium ...on a surface of a patch adjacent the skin..., and applying energy to the patch...disturbing the integrity of the microcapsules, thereby resulting in release of the substance form the microcapsules" as recited in claims 1 and 3.

Moreover, Mitragotri, Royds, and Unger fail to disclose or suggest a method which comprises "delivering an agent encapsulated in microspheres or nanospheres in a patch matrix comprising the use of ultrasound at a resonant frequency between 0.1 and 100 MHz to rupture the microspheres or nanospheres, thereby releasing the agent into the patch matrix" as recited in claim 52.

The cited references also fail to disclose or suggest the "controlled transdermal delivery of an agent encapsulated in microcapsules in a transdermal patch as a result of a controlled activation of the microcapsules in the transdermal patch using an ultrasound source or a heat source" as recited in claim 57.

Claims 4-13, 53, and 58-62 are also not made obvious by Mitragotri, Royds and Unger because their inventive subject matter is within the scope of claims 1, 3, 52, and 57, from which they respectively depend.

Applicant respectfully requests the Examiner to withdraw the obviousness rejection of these claims and allow them.

B. REJECTION OF CLAIMS 2, 14 and 54 UNDER 35 U.S.C. § 103(a) AS UNPAENTABLE OVER MITRAGOTRI, ROYDS, AND UNGER AND FURTHER IN VIEW OF ZEIMER.

The Examiner asserts that Applicant's invention as claimed in claims 2, 14 and 54 is unpatentable over Mitragotri, Royds, and Unger as applied to claims 1, 3-13, 52, 53, and 57-62 and further in view of Zeimer. The Examiner asserts that Mitragotri, Royds, and Unger do not disclose thermal energy applied to a patch to release an encapsulated drug from a microcapsule. The Examiner asserts that Zeimer teaches that lipid vesicles irradiated by a laser beam heat the lipid vesicles causing their rupture. Therefore, the Examiner asserts that the combination of Zeimer with Mitragotri, Royds, and Unger make obvious Applicant's invention as recited in claims 2, 14, and 54 with respect to stimulation by thermal energy.

Applicant respectfully disagrees.

As discussed above in Section A, Mitragotri, Royds, and Unger do not make obvious Applicant's invention. The addition of Zeimer does not eliminate the defects of the other references. Therefore, the combination of Mitragotri, Royds, Unger, and Zeimer does not make obvious Applicant's invention as recited in claims 2 and 14 because the claims depend respectively from independent claim 1 and dependent claim 3 (which depends from 1). Claim 54 recites the subject matter of claim 2 and thus is not made obvious from the combination of Mitragotri, Royds, Unger, and Zeimer.

Applicant respectfully requests the Examiner to withdraw the obviousness rejection of claims 2, 14, and 54.

CONCLUSION

The Examiner is respectfully requested to allow all of the pending claims. If any questions remain, the Examiner is invited to phone Applicant's undersigned attorneys.

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